REMARKS

Pending Claims

Claims 1-2, 4, 11, 15, 19, 25, 26, 28, 29 and 37 are pending in the application.

Claims 11, 15, 19, 25, 26, 28, 29 and 37 are withdrawn from consideration

Claims 1-4 are rejected.

Request for Rejoinder Reminder

Applicants respectfully request rejoinder of method claims upon allowance of the composition claims 1-2 and 4.[1] Towards that end, withdrawn method claims 25-26, 28 and 29 have been amended in a manner consistent with the pending composition claims.

Applicants again[2] request that the subject matter of claims 19 and 37 be included in the initial examination because clearly, if the product of claim 1 is patentable, then the addition of a peptide to the maleimide structure is also patentable.

Applicants additionally request that the subject matter of claim 15 be included in the initial examination because it is clear that if the product of claim 1 is patentable, then specification of the type of carbohydrate core as cyclodextrin is also patentable.

Rejection of Claims and Traversal Thereof

In the August 06, 2008 Office Action:

claims 1-4 were rejected under 35 U.S.C. §103(a).

[1] Rejoinder was previously requested in the response to the July 10, 2007 Office Action and in the response to the September 27, 2007 Office Action.
[2] Inclusion of claims 19 and 37 in the initial examination was previously requested in the response to the July 10, 2007 Office Action and in the response to the September 27, 2007 Office Action.

This rejection is hereby traversed and reconsideration of the patentability of the pending claims is therefore requested in light of the following remarks.

Rejection under 35 U.S.C. §103(a)

Claims 1-4 were rejected under 35 U.S.C. §103(a) as being unpatentable over Brask et al. *Journal of Peptide Science* (2000), Vol. 6, pages 290-299 (hereinafter "Brask") and Nefzi et al. *Tetrahedron Letters* (1995), Vol. 36, pages 229-230 (hereinafter "Nefzi") in combination.

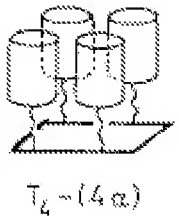
The present invention teaches a maleimide cluster comprising a core carbohydrate molecule wherein at least two maleimide containing groups are attached to the core and optionally comprising a protein attached to the maleimide containing groups. Claim 1 reads as follows.

> 1. A maleimide cluster comprising a core carbohydrate molecule wherein the core is selected from the group consisting of monosaccharides, oligosaccharides, and cyclic oligosaccharides and wherein at least two or more maleimide containing groups are attached to the core, wherein the maleimide containing groups are linked to the carbohydrate core by an alkyl cysteamine linker and optionally comprising a protein that is covalently attached to the maleimide.

Brask describes a process for creating synthetic proteins with a number of features critical to the function as desired and described therein. Initially it should be noted that the core of Brask is a carbohydrate that allows for a rigid ring. The next step in Brask is to provide a linker between the core and a peptide. Brask teaches only a single way to attach this peptide to the core, that being, an oxime bond therebetween. The oxime bond is required because the purpose of the Brask research is to add a C-terminal peptide aldehyde to an aminooxy-functional group attached to a carbohydrate core. However, it should be noted that using the oxime linking bond causes flexibility in the linkage between the core and peptide because the oxime linking bond provides for either a cis or trans positioning of the peptide. Clearly, this additional complexity of forming diverse stereochemistry for the positioning of the proteins deters from any rigidity that may have been gained from the carbohydrate core.

Notably this flexibility of Brask is in stark contrast to the rigid structure of the molecules described in Nefzi. Specifically, Nefzi describes a process for creating synthetic proteins, wherein a peptide is attached directly to a **rigid template to create a predictable and stable structure**. In the example supplied in Nefzi, the maleimide containing molecules are directly attached to a beta turn mimetic acting

as a scaffold for four alpha helix proteins that are **held erect and parallel**, as shown in the illustration below.



Importantly, the structure of Nefzi provides for no types of conformational flexibility.

Applicants note the following factual issues, each of which contributes to the Office's failure to provide a *prima facie* case of obviousness in the present case. Initially, the Office appears to be choosing to disregard differences between the claimed invention and the prior art, even though the Office is mandated to serve as fact finder when resolving the Graham inquires under a 35 U.S.C. § 103(a) rejection. Under Graham, and as required by MPEP §§ 2111 and 2141.02, the Office must ascertain the differences between the claimed invention and the prior art, and must consider both the invention and the prior art as a whole.

Thus, the Office must consider that Nefzi teaches the use of a beta peptidic mimetic template that includes two peptide strings that are bound to an organic ring system. A maleimide containing ester is used to bind to the template and also to a peptide having a thio group. In contrast, Brask teaches the use of a carbohydrate core comprising a linker that includes an aminooxyacetic acid structure that forms an oxime bond between the end amino group of the aminooxyacetic acid structure and an aldehyde containing peptide.

It is incumbent upon the Office to clearly and explicitly state **why** the claimed invention would have been obvious in light of the cited references. According to the Federal Register, Vol. 72, No. 195, (Oct. 10, 2007), pp. 57528-57529, "Rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." In the Office Action of August 06, 2008, the Office offers the rationale that "[s]imple substitution of one known element (i.e., a specific 'linker' or 'template') for another to obtain predictable results renders the instant invention obvious in view of the teachings of the prior art" (August 06, 2008 Office Action, page 6, lines 19-21). This rationale proves obviousness only if "the substitution of one known element for another would have **yielded predictable results to one of ordinary skill in the art at the time of the invention.** If any of these findings cannot be made, then this rationale cannot

be used to support a conclusion" of obviousness" (Federal Register, Vol. 72, No. 195, (Oct. 10, 2007), page 57530).

The Office's use of the phrase "simple substitution" to the act of combining Brask and Nefzi in order to reach Applicants' invention is a gross oversimplification (August 06, 2008 Office Action, page 6, lines 19-21). Even if the isolated elements of an invention are "disclosed" in the prior art, the invention may not be held to be obvious if no enablement is provided for making the invention. The template molecules, reactive groups, and reaction conditions used in Brask and Nefzi are different from one another. The Office has not supplied any details as to how the components described in the two references would be cobbled together to achieve Applicants' invention. "If the prior art of record fails to disclose or render obvious a method for making a claimed compound, at the time the invention was made, **it may not be legally concluded that the compound itself is in the possession of the public**." *In re Hoeksema*, 399 F.2d 269, 274-275, 158 USPQ 597, 601 (CCPA 1968). Also see MPEP § 2144.09(IV).

Finally, the fact that some of the isolated elements of an invention are "disclosed" in the prior art is alone insufficient. The test is not whether some of the isolated "elements" are known, but rather whether the subject matter of the **invention "as a whole," in light of all the teachings of all the cited references in all of their entireties,** would have been obvious to one of ordinary skill in the art at the time the invention was made. Notably, the presently claimed compounds are disclosed **only in the present application**. The claimed compounds **are not** isomers or homologs of any compounds disclosed in either of the references, and there is no evidence that the presently claimed compounds were actually known prior to applicants' work. If there were such known compounds, the Office would have rejected the claimed compounds under a 35 U.S.C. § 102 rejection, but this has not happened. Instead the present "obvious" rejection is based solely on the ground that the combined references **might suggest a process for making the compound.**

Applicants insist that in order to reject the presently claimed compounds on the combined references it is necessary to add one supposition to another. Thus it must first be assumed that one skilled in the art would consider the use of a "carbohydrate core" as a suitable template, then the skilled artisan must take an allylation compound and react same with the carbohydrate core to provide the structure that allows for the photoaddition of a cysteamine structure which in turn allows for a final addition of a maleimide containing compound as in a manner shown in Examples 6 and 7 of the present specification. Thus numerous assumptions must be made with absolutely no guidance from either reference. The Board in *Ex parte McQueen*, 123 USPQ 37 (BPAI 1959) ruled that "A rejection of a claim for a compound on a

reference which does not name that compound, but discloses a process which it is alleged would produce the compound in question cannot, in our opinion, be sustained unless it is clear that the operation of the reference process would certainly produce the compound in question." Clearly in the present situation, this is impossible because the combined references cannot provide any such certainty because they do not in any way teach or suggest all the necessary synthesis methods to generate the presently claimed compounds, and thus, this rejection should be withdrawn.

In light of the foregoing discussion and the fact that (1) the Office has not recognized all of the differences between the invention and the prior art, (2) all of claimed limitations are not disclosed or suggested by the cited combination and (3) no method of making Applicants' invention from the disclosures of Nefzi and Brask is provided, it is clear that the Office has not met its burden of establishing a *prima facie* case of obviousness. Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

Fees Payable

Applicants believe that no fee is due at this time, but authorization is hereby given to charge any deficiency in applicable fees for this response to Deposit Account No. 13-4365 of Moore & Van Allen, PLLC.

Conclusion

Applicants believe this response to the Office Communication fully addresses the issues raised. If any issues remain outstanding incident to the allowance of the application, Examiner Lewis is requested to contact the undersigned attorney at (919) 286-8145.

Respectfully submitted,

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